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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20040316

Application Number: 09/425,075
Filing Date: October 21, 1999
Appellant(s): CHOUDARY ET AL.

James Keddie
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2/23/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

No related appeals or interferences are stated.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims stand or fall together as stated in the Brief.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

6,204,023Robinson et al3-20015,429,925Vanderlaan et al7-1995Horwitz et al., "Secretion of functional antibody and Fab fragment from yeast cells" Proc. Natl. Acad. Sci. USA, Vol85 (November 1988), pages 8678-8682

Cregg et al., "Development of the methylotrophic yeast, Pichia pastoris, as a host system for the production of foreign proteins" Developments in industrial Microbiology Vol29, pp 33-41, 1988

The Invitrogen Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog amendment Notice for pPICZ vectors from 1/15/96)

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Claims 36-40 and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Robinson et al (U.S. Patent 6,204,023, filed 6/6/95).

The claims encompass a method for production of an antibody that binds an antigen comprising culturing a recombinant Pichia pastoris SMD1168 cell comprising a vector comprising a first and second expression cassette wherein the first cassette comprises a Pichia alcohol oxidase promoter and a S. cerevisiae α-factor signal sequence and a second expression cassette comprising the same promoter and signal sequence as the first cassette and culturing and harvesting the antibody wherein the antibody is recovered at more than about 10mg/l wherein the antibody is a humanized antibody. Further claimed is the vector and Pichia cell.

Horwitz et al teach a method for the production of an antibody in S. cerevisiae yeast cells with the vectors comprising cDNA encoding for an antibody, a promoter and transcription terminator, and signal sequence (see abstract and page 8679 and figure 2). Horwitz et al does not teach a recombinant host P. pastoris, SMD1168 transformed with a vector for expression with dual expression cassettes, the Pichia alcohol oxidase promoter, alpha factor signal sequence, AOX1-P promoter, . These deficiencies are made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al.

Cregg et al teach production of foreign proteins in Pichia pastoris with the promoter AOX1.

Robinson et al teach methods of expression of antibodies in yeast with expression plasmids comprising the light chain and heavy chains each attached to a yeast promoter and terminator and are placed on the same plasmid (see column 16, lines 15-20) and yeast is a preferred host because yeast provides substantial advantages for the production of immunoglobulin light and heavy chains because yeast carry out post-translational peptide modifications including glycosylation and a number of recombinant DNA strategies exist which utilize strong promoter sequences and high copy number plasmids which can be used for overt production of the proteins in yeast (see column 15, lines 39-45).

The Invitrogen 1997 Catalog teach high copy number vectors for expression of proteins in P. pastoris SMD1168 and the vectors comprises the inducible AOX1

promoter, a poly cloning site comprising EcoRI, BsmBI, BglII, and BamHI, the alpha-factor signal sequence, and the vector is designed for antibody expression.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an antibody in P. Pastoris comprising a vector comprising a first and second expression cassette in view of Horwitz et al, Cregg et al, Robinson et al, and the 1997 Invitrogen Catalog in order to produce antibodies in P. pastoris.

One of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cell because Horwitz et al teach recombinant production of proteins, specifically, an antibody in S. cerevisiae in general with selection, screening, and purification and testing antigen binding. In addition, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cell in P. pastoris because Cregg et al teach production of heterologous proteins in P. pastoris overcomes the problems associated with producing commercially useful levels of proteins in S. cerevisiae (see page 33, introduction) and the P. pastoris is ideally suited for the production of many heterologous proteins due to the fact that (1) a detailed understanding of the growth characteristics of the organism in high-density fermentors is known, (2) the ability to place foreign DNA into the genome in a precisely controlled manner, and (3) promoters are tightly regulated and efficiently transcribed to produce proteins at high levels. (See page 40). In addition, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cells because the Invitrogen Catalog teach a Pichia expression vector called pPICZ which is

based on homologous recombination comprising; several restriction sites for cloning of recombinant proteins, a promoter (AOX1), termination sequences, selectable markers (zeocin), and alpha-factor secretion signal for expression in P. pastoris of antibodies and the vector is designed for production of proteins as high as grams per liter (see pages 14-15 and 18). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cells because Robinson et al teach production in yeast of chimeric or humanized antibodies using a vector with both a light chain and a heavy chain linked to promoters and terminators in a single plasmid and the vectors can further comprise yeast leader sequences for antibody secretion (see columns 15-16).

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Horwitz et al teach the antibodies produced in yeast were secreted and functional by binding the target antigen (see abstract). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Cregg et al teach the result of the engineered yeast is a yeast that is "easily scaled up from shake-flask to large-volume, high-density cultures with little change in the kinetics of product synthesis" (see abstract) Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because the Invitrogen Catalog teach that the expression vector and P.

pastoris makes "an ideal tool for laboratory research as well as industrial applications" (see page 14).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Argument

The Brief states on page 7 that in order to render the claims obvious there must be a suggestion to use a dual expression cassette vector to express an antibody in Pichia as well as a dual expression cassette and recombinant Pichia containing such. The Brief argues on page 8 that the references provide no motivation to make a dual expression cassette for expression of an antibody in Pichia and Robinson at no point suggests that a dual expression cassette can be used in Pichia or even mentions Pichia and the word "Yeast" as used in Robinson refers to S. cerevisiae and does not encompass Pichia and this is supported by the analysis of Robinson and the Declaration by Dr. Trager (see page 9-12 of response). In the Declaration Dr. Trager states that a skilled person would not equate "yeast" with "Pichia" in Robinson because "yeast" can encompass over 25,000 species and at no point in the disclosure does Robinson suggest that "yeast" encompasses anything other than S. cerevisiae. In addition, Dr. Trager concludes that any suggestion by Robinson to use a dual expression cassette to express an antibody in yeast is a suggestion to express an antibody in S. cerevisiae and since S. cerevisiae and Pichia are different species, a

skilled person would find no suggestion in Robinson to use dual expression cassettes for production of an antibody in Pichia.

In response to this argument, the term "yeast" can encompass Pichia and in fact does and one reading the art of the invitrogen catalog or the Cregg reference in combination with the cited references would have motivation to use the Pichia strain as well as the expression vectors described in the Invitrogen catalog such as pPICZalpha (which is the exact vector that appellant's used) for the expression of the antibody because of the benefits recited for the Pichia expression system catalog or in the Cregg et al reference. One skill in the art at the time of the claimed invention would have the references available to them such as Cregg et al and the Invitrogen catalog and would have seen the advantages of the Pichia strain for expression of proteins in this strain. The Pichia system in the Invitrogen catalog was developed for high levels of expression of proteins and this advantage alone would have motivated the skilled artisan to pick the Pichia system for expression. Appellant's arguments seem to be directed to the Robinson reference by itself in saying that there is no motivation to produce a dual expression cassette in Pichia in the reference. In response to this argument, although Robinson does not teach Pichia, which is why this rejection is a 103 not a 102 rejection and depends on a combination of references, there is motivation to pick Pichia for the strain and to produce a dual expression cassette because Robinson specifically teaches heavy and light chains each attached to a promoter and terminator sequence (see column 16, lines 15-20) as constructed in appellant's vector (see Figure 1 of the instant

specification). Thus, it would have been obvious to construct the vector with dual cassettes in view of Robinson and the Invitrogen catalog.

The Brief argues on pages 12-13 that the art provides no reasonable expectation of success and cites Pennell as stating that "there are no reports of proteins greater than 117 kDa being expressed in P. pastoris" and since antibodies are greater than 117 kDa the disclosure would lead a skilled person away from expressing a whole antibody.

In response to this argument, the Invitrogen catalog cites a wide variety of proteins that have been expressed in Pichia and it appears that one, GP-120, is greater than 117 kDa (see page or section 14). In addition, there is nothing in the cited reference of Pennell or the prior art of record that excludes the expression of an antibody or a protein as large as an antibody, Pennell just acknowledges that to their knowledge, larger proteins of 117 kDa have not been reported.

The Brief on page 13 argues that Holliger teaches that two chain antibody formats require that the two chains be cloned and transformed separately, therefore, single expression cassettes are required if expression of two different chains of an antibody is desired. It is noted that the Holliger reference was published in 2002 and would not have been available as prior art at the time the claimed invention was made. As such the skilled artisan would not have considered it because it was not available and is a moot point in this Brief.

The Brief argues on page 13-14 that Dr. Trager's declaration states that S. cerevisiae and Pichia are very different and expression in S. cerevisiae (if shown) does not produce a reasonable expectation of success to produce the antibody in Pichia. In

response to this argument, the statement is "reasonable expectation of success" not assured success and as such one would have a reasonable expectation of success because the Pichia system of both Cregg and the Invitrogen catalog have been optimized for the production of proteins in Pichia at high levels and Robinson et al teach that "inclusion of both heavy and light chain chimeric genes in the same plasmid allows for the introduction into transfected cells of a 1:1 gene ratio of heavy and light chain genes leading to a balanced gene dosage" (see column 35, lines 59-62). Thus, Robinson clearly realized the importance of balanced gene dosage and one skilled in the art would have been motivated to produce a dual expression cassette for expression in Pichia in view of the Invitrogen catalog and Cregg et al.

The Brief argues on page 14 that even if one would interpret the word "yeast" broadly to include Pichia and if Robinson did teach successful expression of an antibody using dual expression cassettes in S. cerevisia, one skill in the art would not be motivated to use a dual expression cassette in Pichia and as noted by Dr. Trager, there would be no reasonable expectation of success. In response to this these issues have been addressed above and in addition, "yeast" can be broadly interpreted as Pichia and is.

The Brief on page 15 argues specific assertions by the Examiner, specifically the Invitrogen catalog does not disclose a dual expression cassette and so how can it provide any motivation. In response to this argument, it appears that Appellant's are arguing the reference separately when the rejection is based on a combination of references. The invitrogen catalog provides motivation to use the Pichia expression

system for high production of proteins in Pichia and Robinson provides motivation to use dual expression cassettes as stated above.

The Brief argues on page 15-16 that the examiner finds appellant's arguments regarding the teachings of Holliger unconvincing and rebuts this by saying Dr. Trager states that in no uncertainty Holliger directs one away from the invention. In response to this argument, again the Holliger reference would not have been available to the skilled artisan at the time of the invention and the argument is moot.

II. Claims 36-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (PNAS 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96), Robinson et al (U.S. Patent 6,204,023, filed 6/6/95) and Vanderlaan et al (U.S. Patent 5,429,925, issued 7/4/95).

Claims 36-40 and 42-49 have been described supra. Claim 41 recites wherein the antibody binds dioxin.

Horwitz et al has been described supra. What Horwitz does not teach has been described supra and in addition Horwitz does not teach an antibody which specifically binds dioxin. The deficiencies of Horwitz et al is made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, Robinson et al, and Vanderlaan et al.

Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al have been described supra.

Vanderlaan et al teach the anti-dioxin antibody DD1.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an anti-dioxin antibody from the DD1 hybridoma in Pichia with an expression cassette comprising a light and heavy chain in view of Horwitz et al, Cregg et al , the Invitrogen 1997 Catalog, Robinson et al, and Vanderlaan et al in order to produce the antibody in Pichia.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method with an anti-dioxin antibody in Pichia because Horwitz et al, Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al provide motivation and reasonable expectation of success as stated above in the above rejection. It would have been obvious to produce high levels of expression of the anti-dioxin antibody of Vanderlaan et al because the anti-dioxin antibody "permits detection of dioxin contaminants in industrial environmental samples" and large amounts of this antibody would have been needed to analyze many samples.

Response to Arguments

The Brief argues on page 16-17 that the errors in the rejection here are the same as those above for issue I and Vandelaan only discloses an antibody to dioxin and does not cure the deficiencies of the rejection. In response to this argument, the supposed errors are addressed above for Issue I and Vanderlaan does not have to cure the supposed deficiencies except for providing a dioxin antibody.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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SUPERVISORY PATENT EXAMINER
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Respectfully submitted,

Larry Helms
March 16, 2004

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